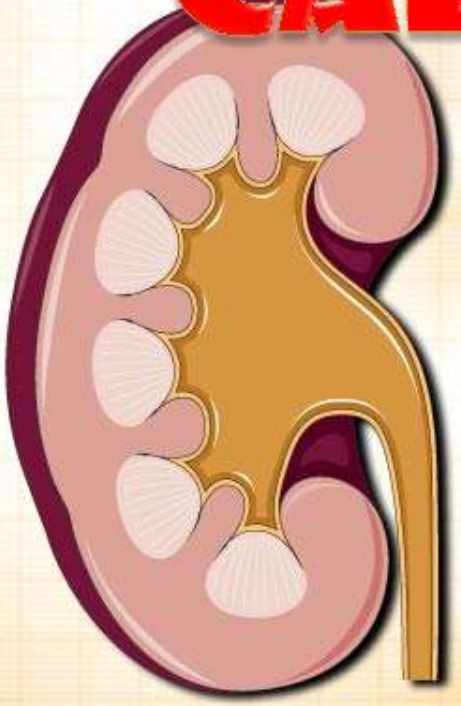
CKD-MBD

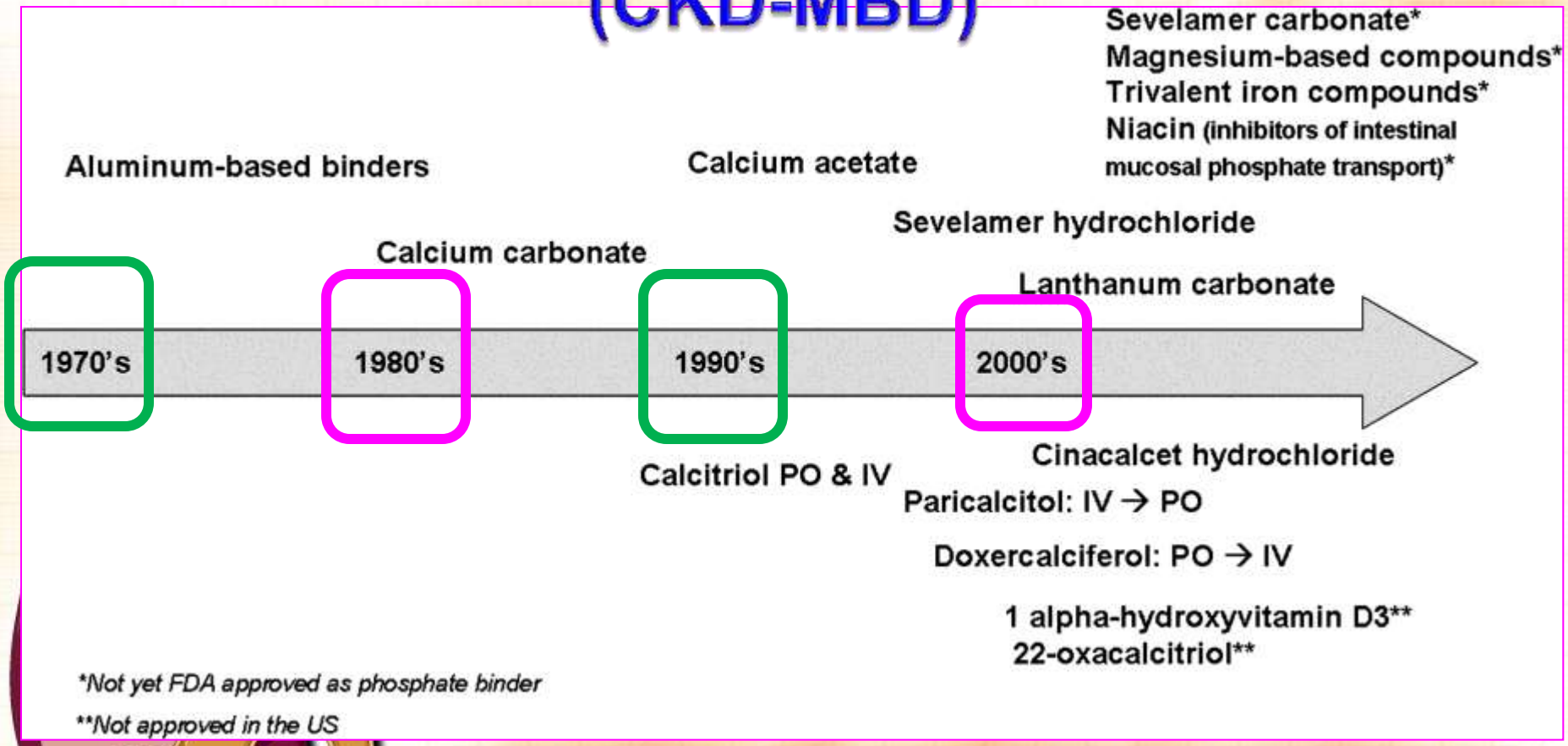
ROLE OF

CALCIMIMETICS



ESSAM NOUR ELDIN MD
NEPHROLOGY DPT
ASU

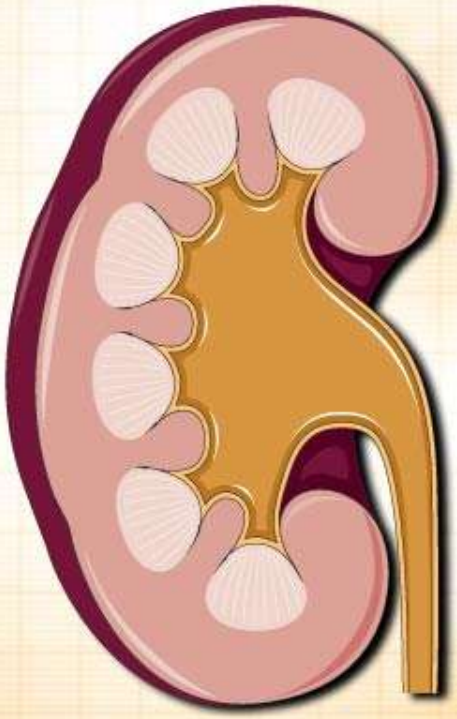
Timeline of various treatments for mineral and bone disorders in chronic kidney disease (CKD-MBD)

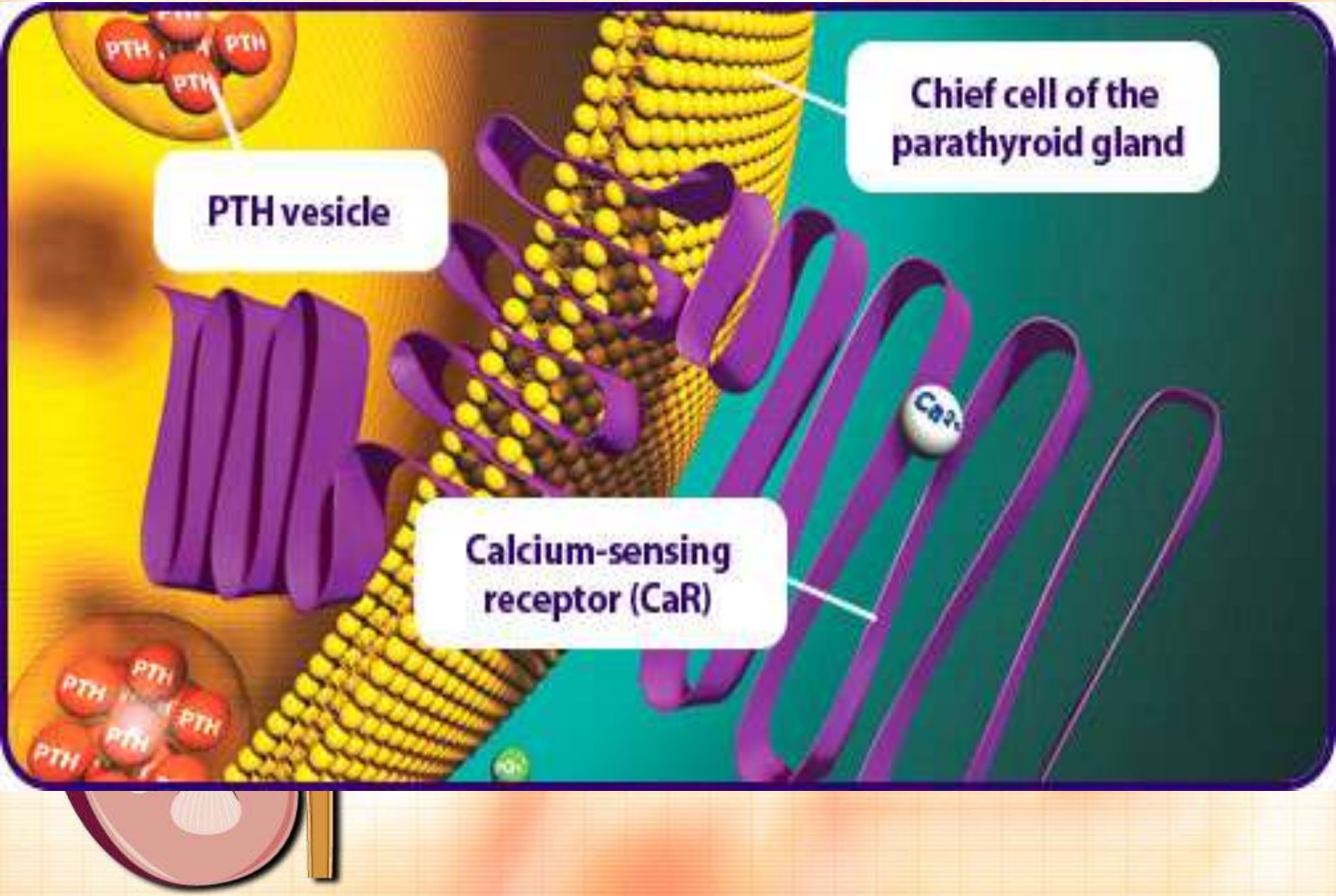


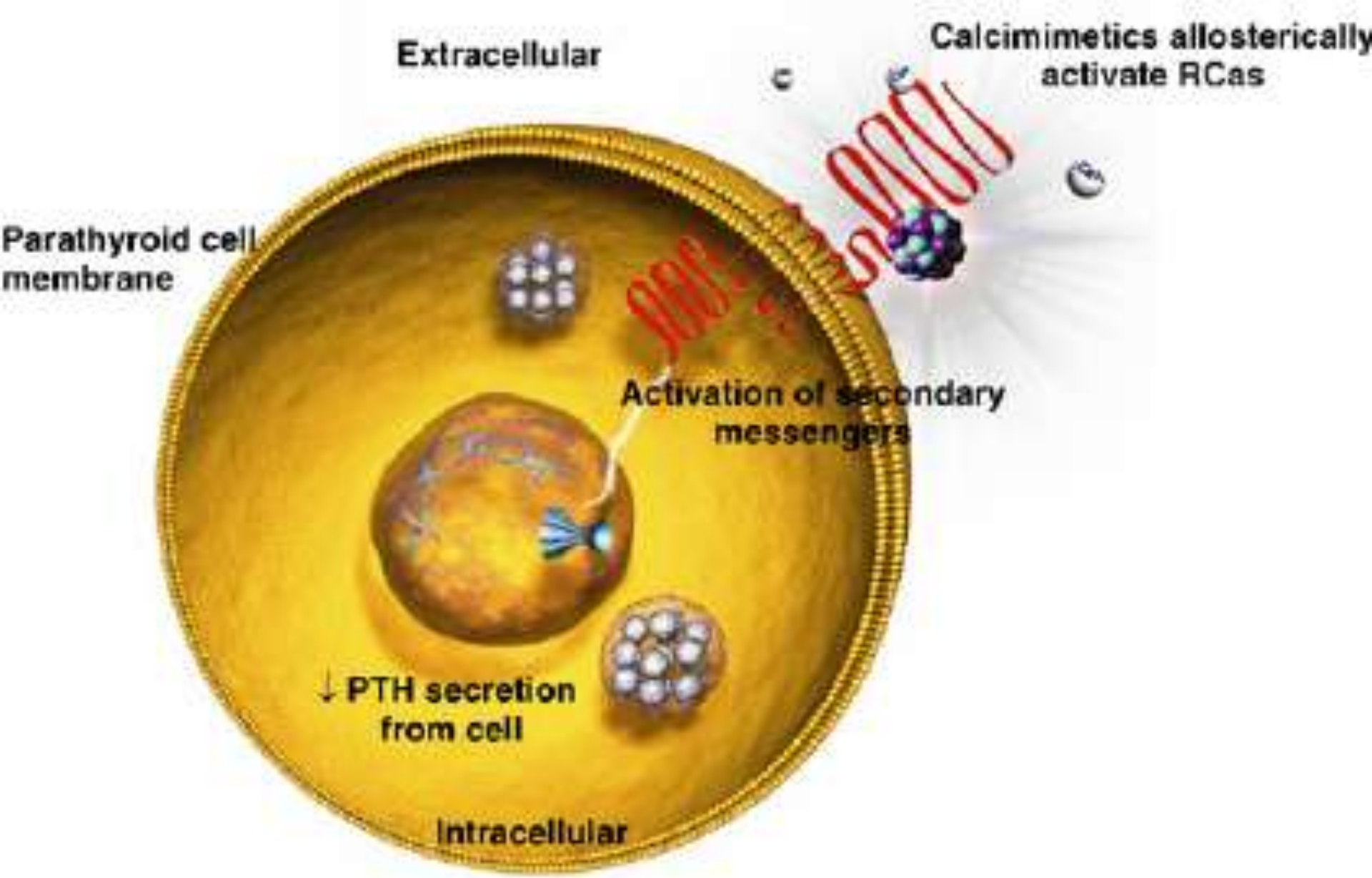
Kovesdy, C. P. et al. Clin J Am Soc Nephrol 2008;3:168-173

CJASN

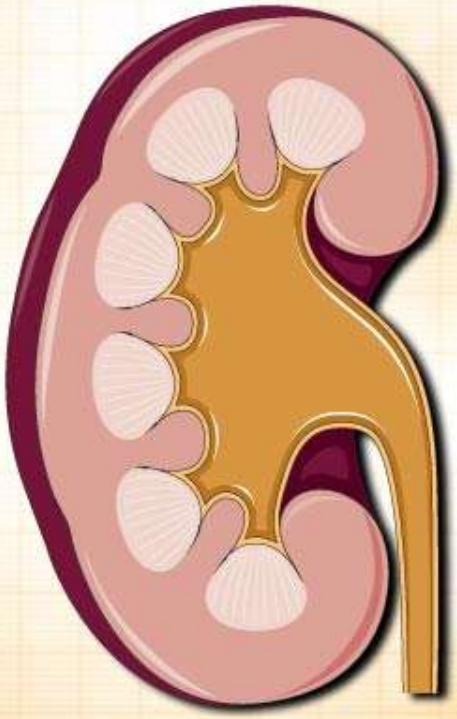
Brown EM, Gamba G, Riccardi D *et al.*
Cloning and characterization of an extracellular Ca(2+)-sensing receptor from bovine parathyroid . *Nature* 1993 ;**366**: 575 –580 .




PTH vesicle
Chief cell of the parathyroid gland
Calcium-sensing receptor (CaR)
PTH
PTH
PTH
PTH
PTH
PTH
PTH

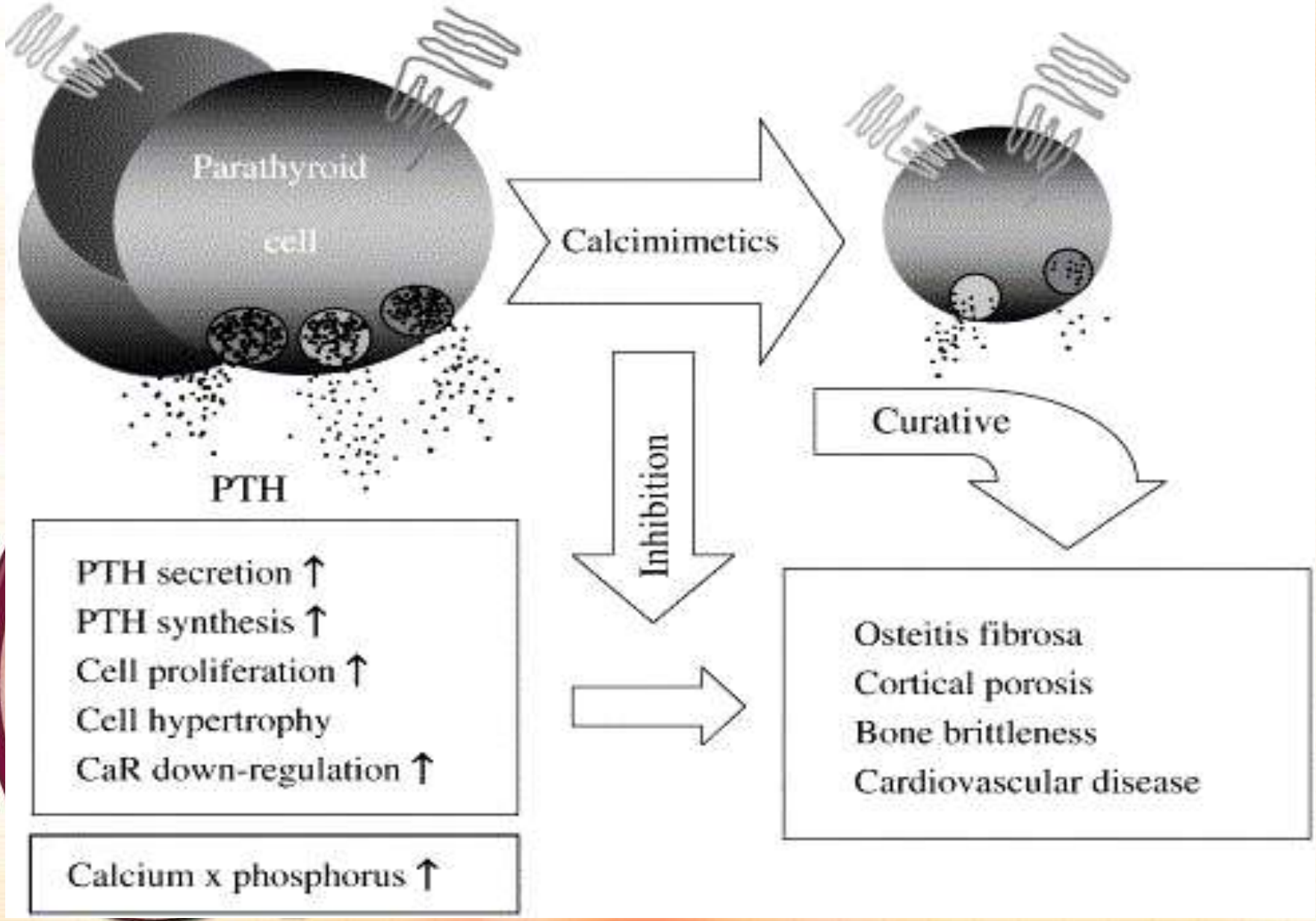

Extracellular
Calcimimetics allosterically activate RCas
Parathyroid cell membrane
Activation of secondary messengers
↓ PTH secretion from cell
Intracellular

The introduction of calcimimetics was a major breakthrough in the treatment of secondary HPT.

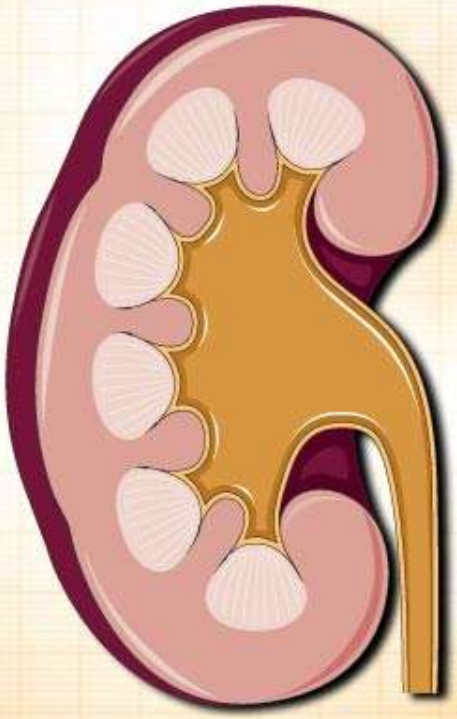


These compounds increase the sensitivity of the calcium sensing receptor (CaR) to extracellular calcium.

Secondary HPT

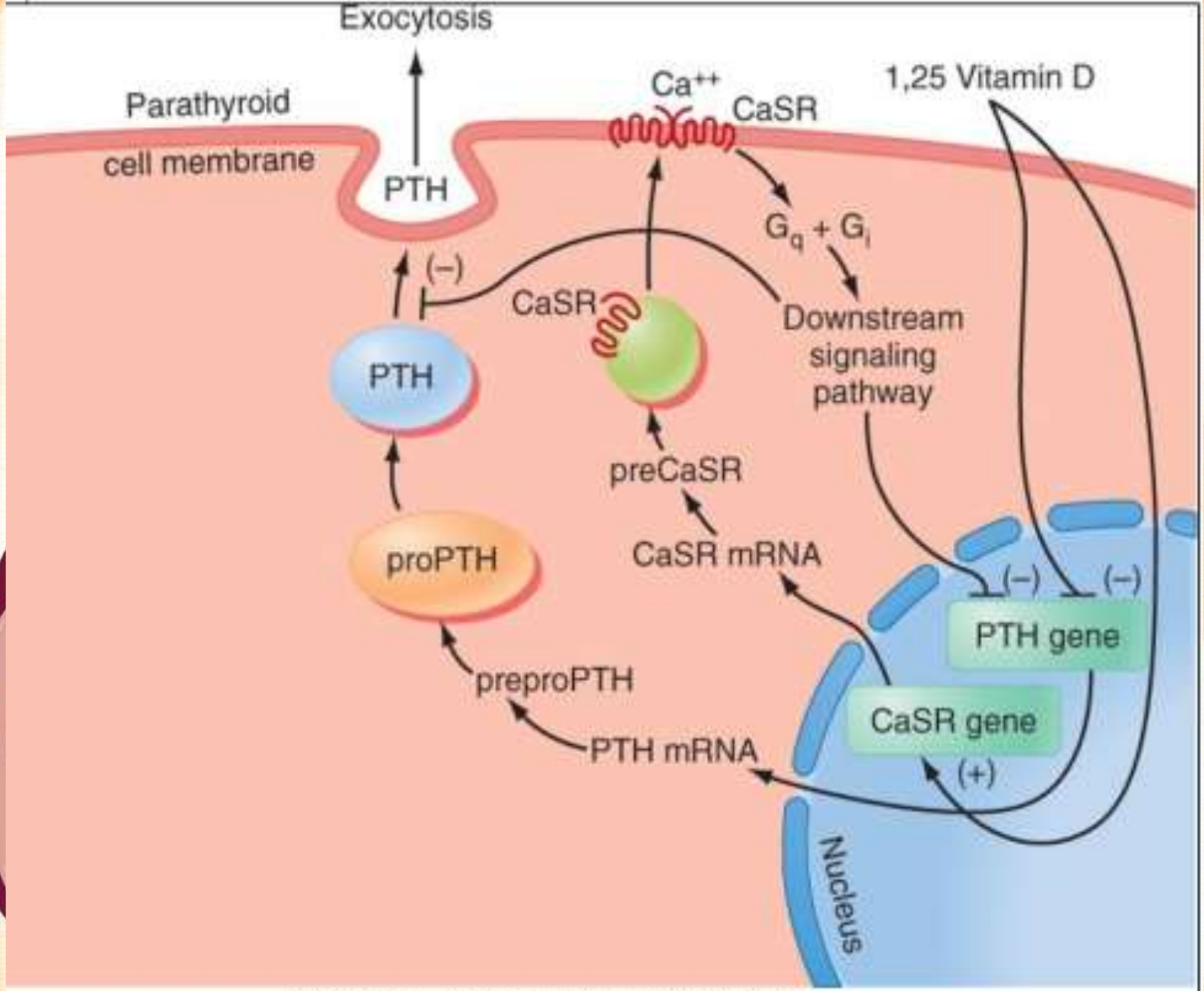


By increasing the sensitivity of the CaR to eCa2+, cinacalcet shifts the Ca-PTH concentration-response curves to the left and reduces the "set point" for Ca-regulated PTH secretion . Cinacalcet decreases the secretion of PTH in a dose-dependent manner and diminishes serum Ca concentration.



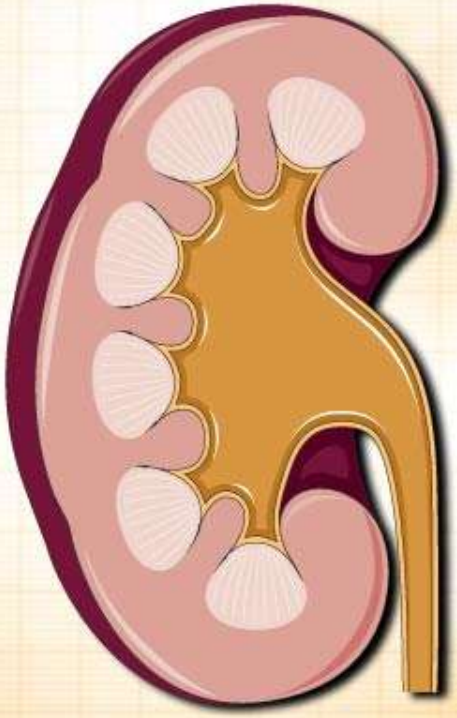
Calcimimetic Compounds for Treating Hyperparathyroidism

- reversible "chemical parathyroidectomy"
- inhibit PTH secretion
- inhibit PTH synthesis
- inhibit parathyroid proliferation (hyperplasia)
- no development of tolerance
- lower Ca x P product
- can cause intermittent changes in PTH levels



Koeppen & Stanton: Berne and Levy Physiology, 6th Edition.

- In contrast to vitamin D, which suppresses PTH at the cost of concomitant increases in serum calcium and phosphate levels, **cinacalcet generally results in significant and sustained decreases in levels of serum PTH, calcium, phosphate, and calcium × phosphate product.**



Comparative Properties of Calcimimetic Compounds and Calcitriol or its Analogs

Calcimimetic

- acts on cell surface receptor
- inhibits PTH secretion and synthesis
- rapid onset (minutes) and recovery (hours or days)
- decreases Ca x P product

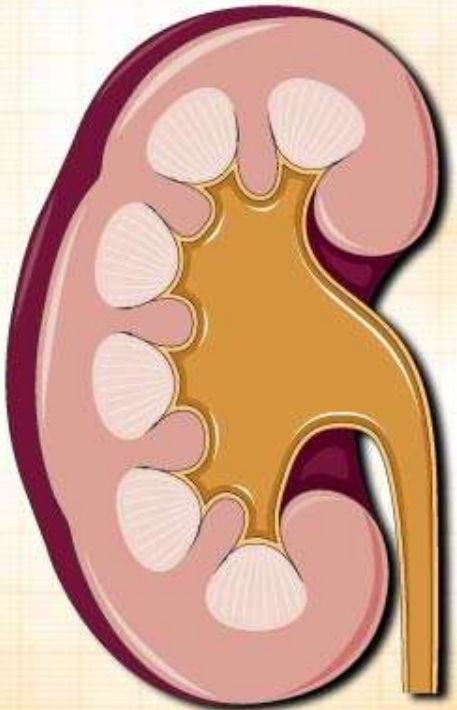
Vitamin D

- acts on genomic receptor
- inhibits PTH synthesis
- slow onset and recovery (days to weeks)
- increases Ca x P product

Factors that regulate FGF-23 levels in CKD

Increase FGF-23

- Parathyroid hormone
- Bone remodelling and the release of low-molecularweight fibroblast growth factors
- Phosphorus load
- Vitamin D metabolites
- Calcium
- Acidosis
- Iron treatment

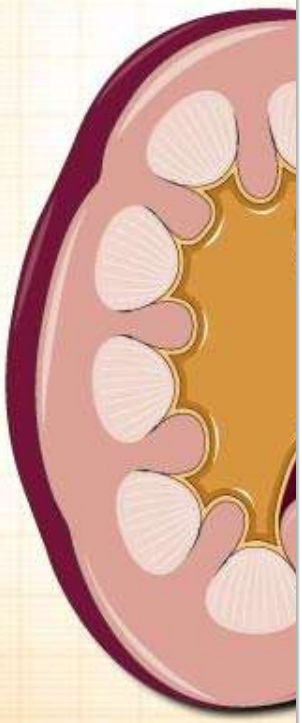


Decrease FGF-23

- Phosphorus binders
- Calcimimetics
- Parathyroidectomy

Silver, J. & Naveh-Many, T. Nat. Rev. Nephrol. 9, 641–649 (2013);

JCI 2011 IMPACT FACTOR: 13.069 FREE ACCESS TO ALL RESEARCH
The Journal of Clinical Investigation



Published in Volume 121, Issue 11 (November 1, 2011)
J Clin Invest. 2011;121(11):4393–4408. doi:10.1172/JCI46122.

Research Article

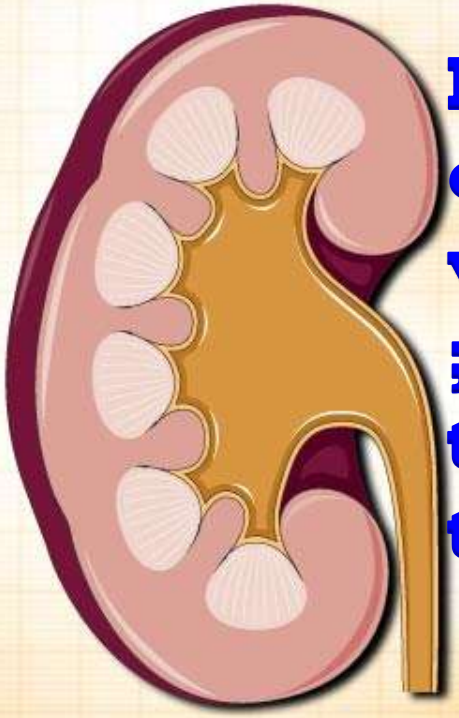
FGF23 induces left ventricular hypertrophy

Christian Faul[1,2], Ansel P. Amaral[1,2], Behzad Oskouei[3], Ming-Chang Hu[4,5,6], Alexis Sloan[1,2], Tamara Isakova[1], Orlando M. Gutiérrez[7], Robier Aguillon-Prada[1], Joy Lincoln[8], Joshua M. Hare[3], Peter Mundel[9], Azorides Morales[10], Julia Scialla[1], Michael Fischer[11,12], Elsayed Z. Soliman[13], Jing Chen[14], Alan S. Go[15], Sylvia E. Rosas[16], Lisa Nessel[17], Raymond R. Townsend[16], Harold I. Feldman[16,17], Martin St. John Sutton[18], Akinlolu Ojo[19], Crystal Gadegbeku[20], Giovana Seno Di Marco[21], Stefan Reuter[21], Dominik Kentrup[21], Klaus Tiemann[22], Marcus Brand[21], Joseph A. Hill[4,23], Orson W. Moe[4,6,24], Makoto Kuro-o[6,25], John W. Kusek[26], Martin G. Keane[18] and Myles Wolf[1]

[1]Division of Nephrology and Hypertension, Department of Medicine,
[2]Department of Cell Biology and Anatomy, and
[3]Interdisciplinary Stem Cell Institute, University of Miami Miller School of Medicine, Miami, Florida, USA.
[4]Department of Internal Medicine,
[5]Department of Pediatrics, and
[6]Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center, Dallas, Texas, USA.
[7]Division of Nephrology, Department of Medicine, School of Medicine and Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama, USA.
[8]Department of Molecular and Cellular Pharmacology and Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida, USA.
[9]Renal Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA.
[10]Department of Pathology, University of Miami Miller School of Medicine, Miami, Florida, USA.
[11]Department of Medicine, Jesse Brown VA Medical Center and University of Illinois Medical Center, Chicago, Illinois,

FGF 23

In epidemiologic studies, increased levels of FGF-23 have been positively related with mortality in dialysis patients.



FGF-23 has also been related to cardiovascular events ;left ventricular hypertrophy ;endothelial dysfunction ;and total body atherosclerosis in the general population .

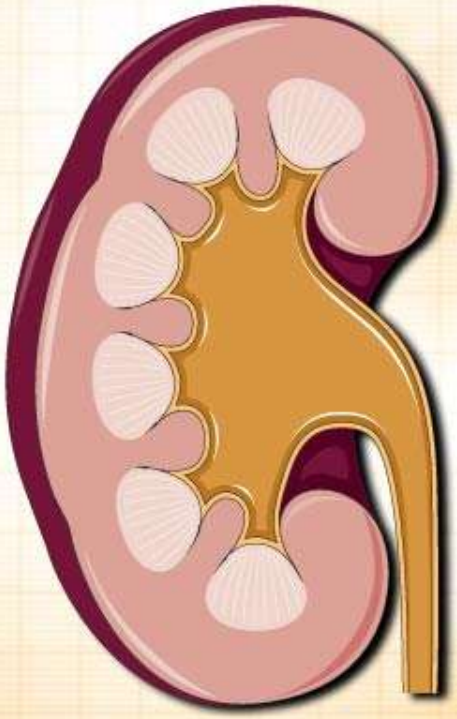
The NEW ENGLAND JOURNAL of MEDICINE

April 2004

ORIGINAL ARTICLE

Cinacalcet for Secondary Hyperparathyroidism in Patients Receiving Hemodialysis

Geoffrey A. Block, M.D., Kevin J. Martin, M.B., B.Ch., Angel L.M. de Francisco, M.D., Stewart A. Turner, Ph.D., Morrell M. Avram, M.D., Michael G. Suranyi, M.D., Gavril Hercz, M.D., John Cunningham, D.M., Ali K. Abu-Alfa, M.D., Piergiorgio Messa, M.D., Daniel W. Coyne, M.D., Francesco Locatelli, M.D., Raphael M. Cohen, M.D., Pieter Evenepoel, M.D., Sharon M. Moe, M.D., Albert Fournier, M.D., Johann Braun, M.D., Laura C. McCary, Ph.D., Valter J. Zani, Ph.D., Kurt A. Olson, M.S., Tilman B. Drüeke, M.D., and William G. Goodman, M.D.



conclusions

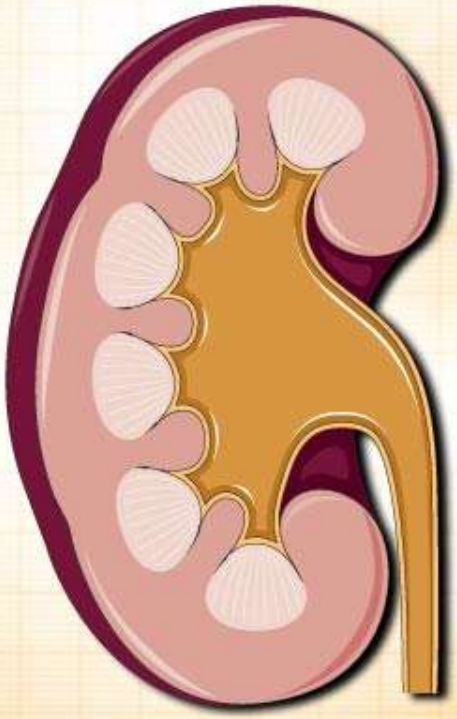
Cinacalcet lowers parathyroid hormone levels and improves calcium–phosphorus homeostasis in patients receiving hemodialysis who have uncontrolled secondary hyperparathyroidism.

Calcimimetics: a remedy for all problems of excess parathyroid hormone activity in chronic kidney disease?

William G. Goodman

Division of Nephrology, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

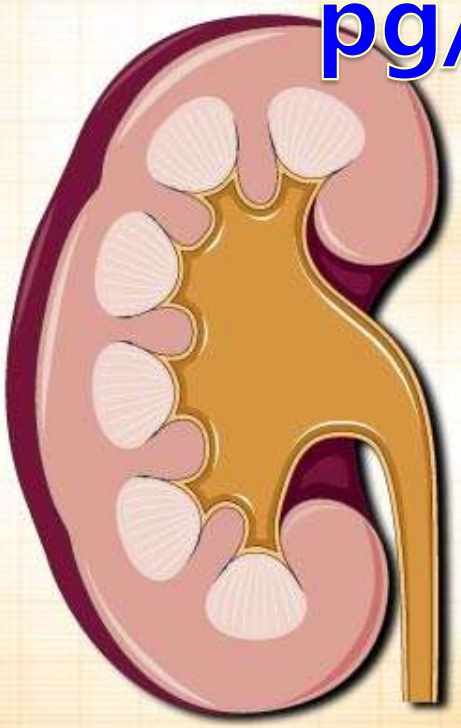
Curr Opin Nephrol Hypertens 14:355–360. # 2005



- **PTH Target.**

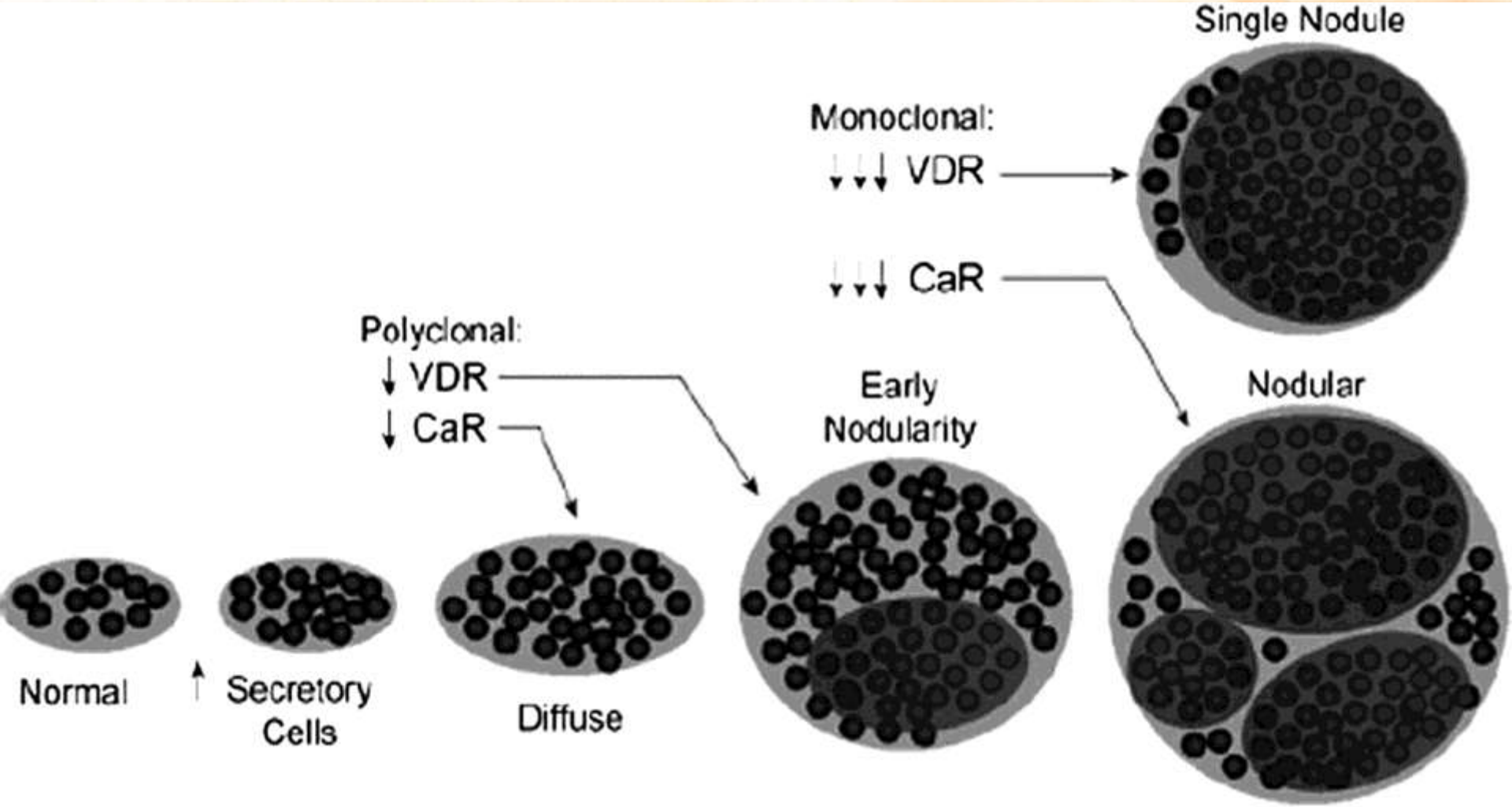
- **US KDOKI.**

between 150 and 300 pg/ml.

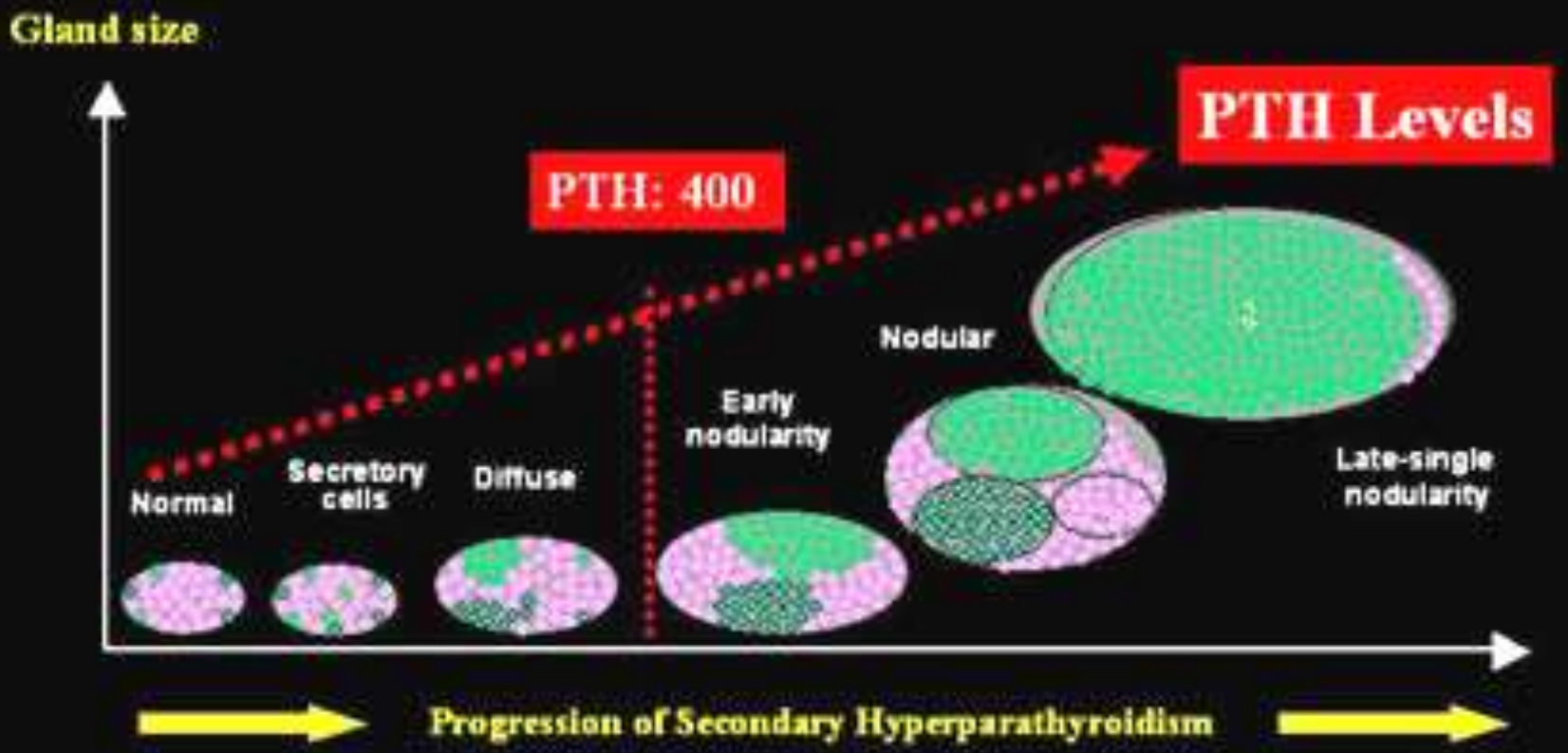


- **KDIGO.**

intact PTH levels at *2–9 times the upper limit of normality* for a particular PTH assay


Single Nodule
Monoclonal:
↓↓↓ VDR
↓↓↓ CaR
Polyclonal:
↓ VDR
↓ CaR
Early Nodularity
Nodular
Normal
Secretory Cells
Diffuse

Progression of Secondary Hyperparathyroidism

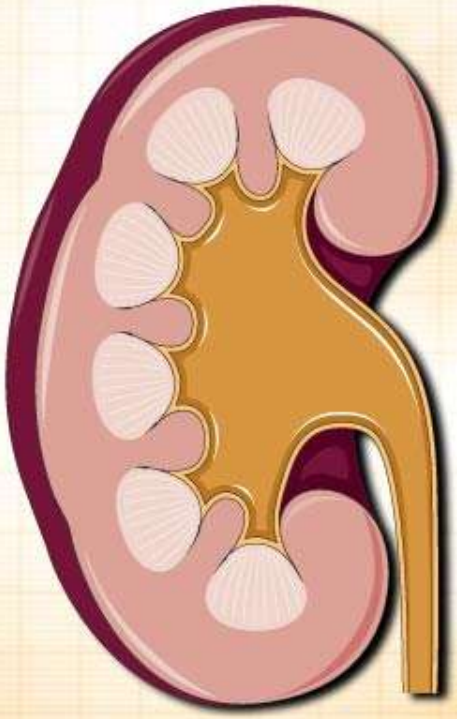


Adapted from Torregrosa V et al. Curr Opin Nephrol Hypertens 1996;5:336-41

Santamaria I , Cannata J et al, Kidney Int 2005

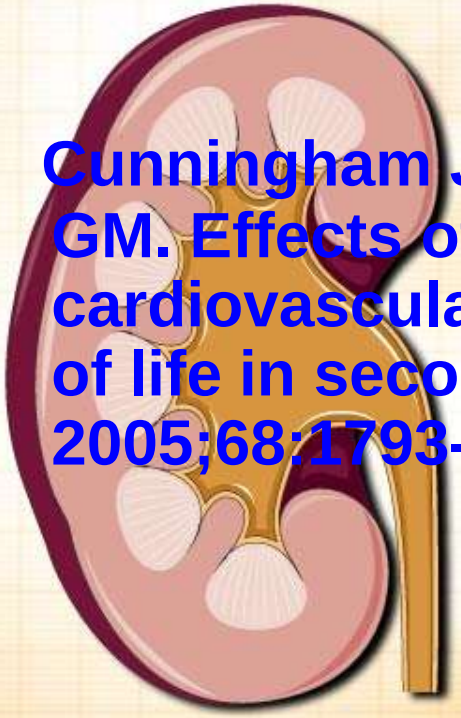
CALCIMIMETICS IN CKD-MBD.

BENEFITS



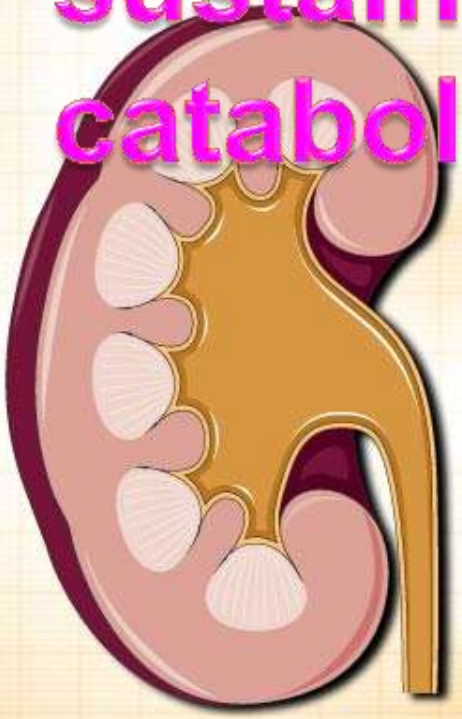
- Reducing circulating levels of laboratory abnormalities:PTH,Ca, P, and the Ca x P product.
- FGF23.
- Parathyroidectomy.
- Fractures.
- CUA.

- **A recent combined analysis of 4 trials found that cinacalcet, compared with placebo in patients with ESRD and uncontrolled secondary hyperparathyroidism, decreased the risk for parathyroidectomy by 93%.**



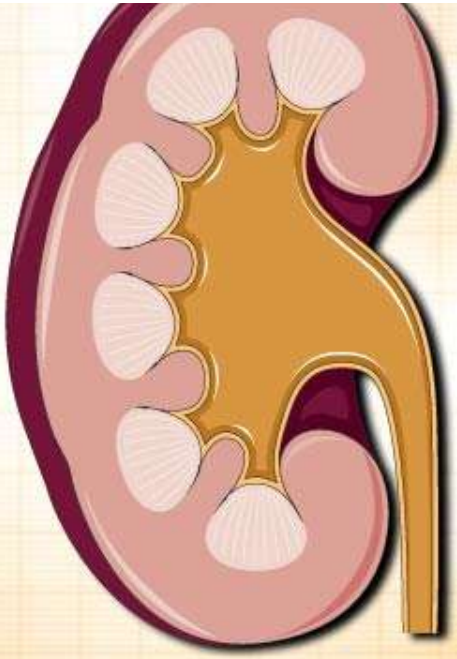
Cunningham J, Danese M, Olson K, Klassen P, Chertow GM. Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. Kidney Int 2005;68:1793-1800.

- Calcimimetics may prove to have an anabolic role in ABD (circadian PTH release is anabolic for bone, whereas sustained PTH release is catabolic).

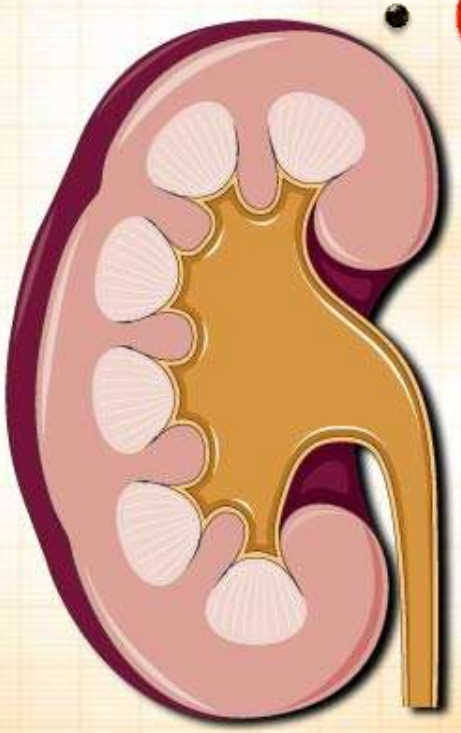


KDIGO

4.2.4. In patients with CKD stage 5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH (2B).



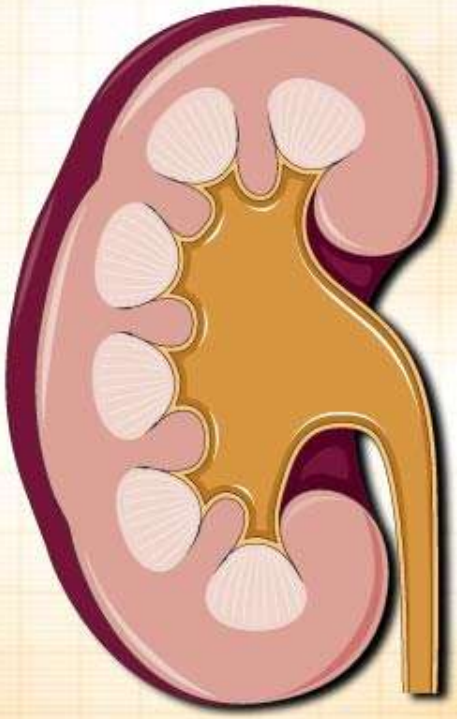
- **Combination of several treatments acting on different pathways may become the best approach to the complex CKD-MBD**
- **Calcimimetics :**
  - **May be used in patients without severe secondary hyperparathyroidism (specially if they have high serum calcium and phosphorus values)**



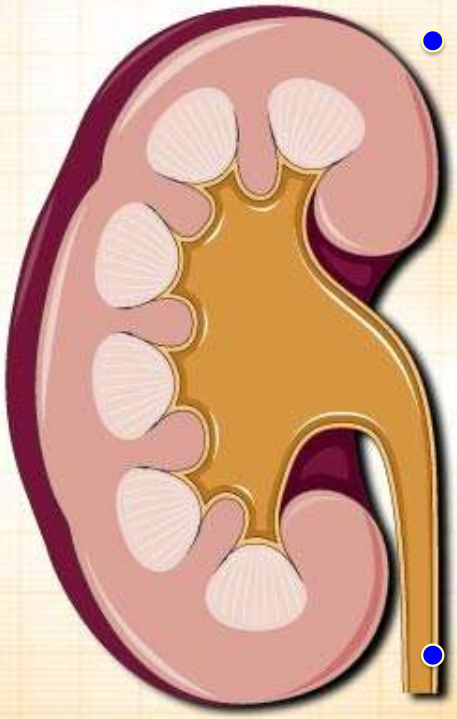
National Institute for Health and Clinical Excellence. January 2007

Dosing: cinacalcet (Mimpara® UK, Sensipar® USA)

Oral; initially, 30mg od, increased incrementally (60mg, 90mg, 120mg, 180mg), as necessary, to maintain target PTH. Check Ca^{2+} 2 weeks after starting treatment and after any dose change. Hypocalcaemia may require dose reduction. Ca^{2+} usually checked monthly for first 6 months and PTH 2–3-monthly.



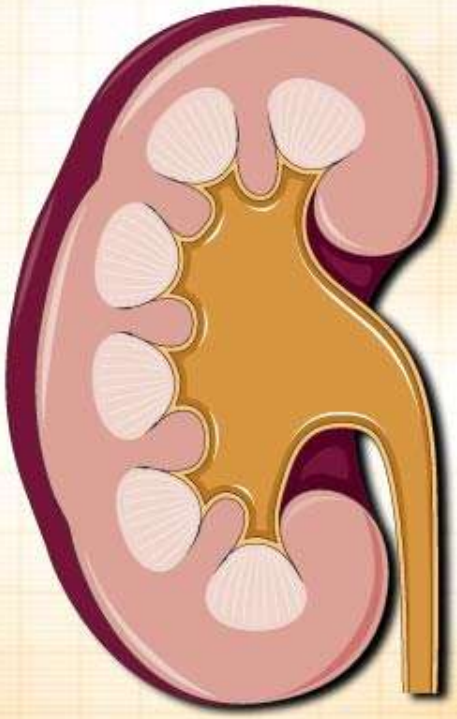
- PTH should be measured 1–4 weeks after initiation or dose adjustment of cinacalcet and every 1–3 months during maintenance.



- PTH should be measured at least 12 hours after dosing with cinacalcet because a rapid nadir for PTH concentration occurs approximately 3 hours after
- Dosing.

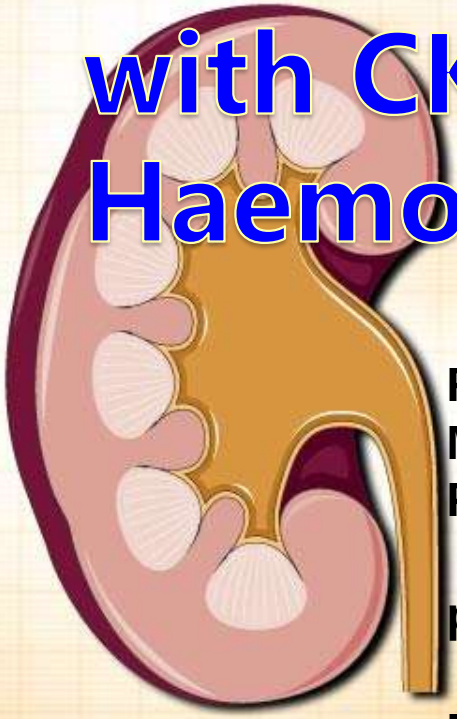
CALCIMIMETICS IN CKD-MBD.

DRAWBACKS



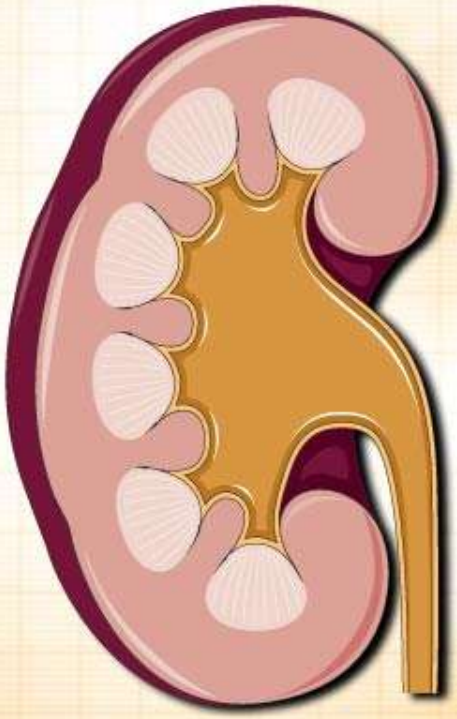
- High cost.
- Side-effects.
- Non-proved hard outcomes or survival benefits.

ADVANCE (A Randomized Study to Evaluate the Effects of Cinacalcet Plus Low- Dose Vitamin D on Vascular Calcification in Subjects with CKD Receiving Haemodialysis) .



Raggi P, Chertow GM, Torres PU, Csiky B, Naso A, Nossuli K, Moustafa M, Goodman WG, Lopez N, Downey G, Dehmel B, Floege J; ADVANCE Study Group: The ADVANCE study: A randomized study to evaluate the effects of cinacalcet plus low-dosevitamin D on vascular calcification in patients on hemodialysis.
Nephrol Dial Transplant 26: 1327–1339, 2011

EVOLVE
(Evaluation of Cinacalcet Therapy to Lower CV Events)



Chertow GM, Block GA, Correa-Rotter R, Dru¨eke TB, Floege J,Goodman WG, Herzog CA, Kubo Y, London GM, Mahaffey KW,Mix TCH, Moe SM, Trotman M-L, Wheeler DC, Parfrey PS; EVOLVE Trial Investigators: Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. N Engl J Med 367: 2482–2494, 2012

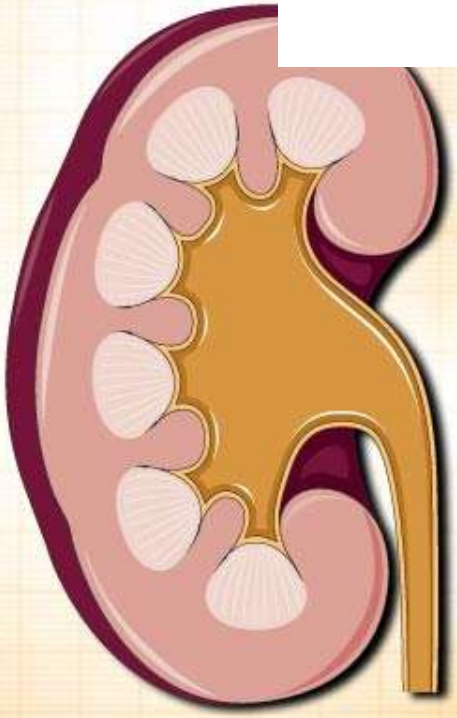
The NEW ENGLAND JOURNAL of MEDICINE

december 27, 2012

ORIGINAL ARTICLE

Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis

The EVOLVE Trial Investigators*



Conclusions

In an unadjusted intention-to-treat analysis, cinacalcet did not significantly reduce the risk of death or major cardiovascular events in patients with moderate-to-severe secondary hyperparathyroidism who were undergoing dialysis.

Nephrol Dial Transplant (2015) 30: 698–700
doi: 10.1093/ndt/gfv050
Advance Access publication 4 March 2015

ndt
Nephrology Dialysis Transplantation

NDT Perspectives

Should patients with CKD stage 5D and biochemical evidence of secondary hyperparathyroidism be prescribed calcimimetic therapy? An ERA-EDTA position statement

David Goldsmith[1], Adrian Covic[2], Marc Vervloet[3,4], Mario Cozzolino[5] and Ionut Nistor[2,6] for the Chronic Kidney Disease-Mineral Bone Disease (CKD-MBD) working group and the European Renal Best Practice (ERBP) advisory board

An ERA-EDTA position statement

Recommendations

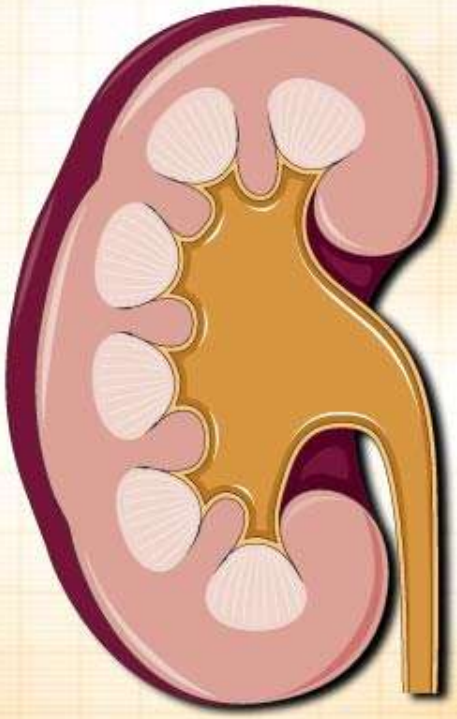
1. We do not recommend routine use of calcimimetic therapy to improve survival in patients with CKD stage 5D and biochemical evidence of secondary hyperparathyroidism (1A).

2. There is insufficient evidence whether parathyroidectomy or medical intervention with cinacalcet or standard care or a combination thereof should be preferred to control secondary hyperparathyroidism in patients with CKD stage 5D.

Nephrol Dial Transplant (2015) 30: 698–700

CALCIMIMETICS IN CKD-MBD.

- Side-effects.



- Nausea and Vomiting.
- Hypocalcemia:

-seizures.

-QT Prolongation.

- Drug interactions.
- PTH Oversuppression.

Measures for the control of cinacalcet-related nausea and vomiting

Measure
Tell the patient that cinacalcet is not an ulcer-inducing drug and explain the importance of the CKD-MBD treatment, including a potential beneficial cardiovascular effect
Give cinacalcet with the main meal after dialysis
Try cinacalcet in the evening
Earlier use will allow lower doses
Do not give up immediately if only mild/moderate symptoms are present
Decrease or fractionate the dose if symptoms appear after a dose escalation
Caution is advised with antiemetics, including metoclopramide (QT prolongation)

Drugs Interactions

- **Drugs that increase cinacalcet levels**

Ketoconazole, itraconazole, voriconazole, telithromycin, ritonavir

- **Drugs which decrease cinacalcet levels**

Rifampicin

- **Potential interactions**

Stopping or starting cigarette smoking, fluvoxamine, ciprofloxacin

- **QT interval-affecting drugs** (http://www.QTdrugs.org; http://www.sads.org.uk/drugs_to_avoid.htm) in high-risk patients

- **Dose adjustment required (due to inhibition of cytochrome P450 by cinacalcet) for**

Flecainide, propafenone, metoprolol, amitriptyline, desipramine, nortriptyline, clomipramine

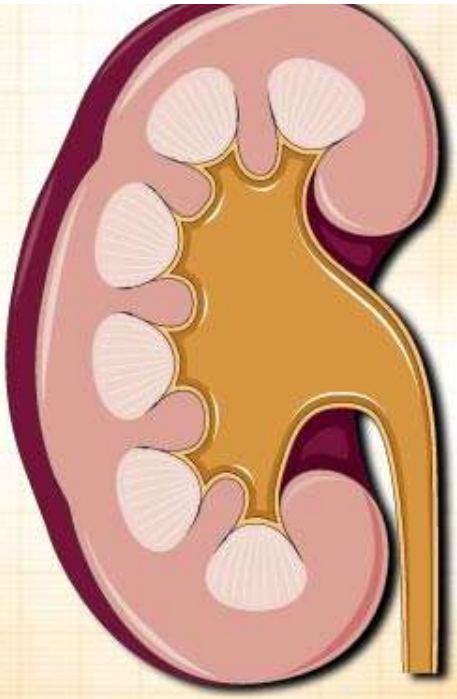
Table 4. Management of hypocalcemia according to the 2013 Summary of Product Characteristics

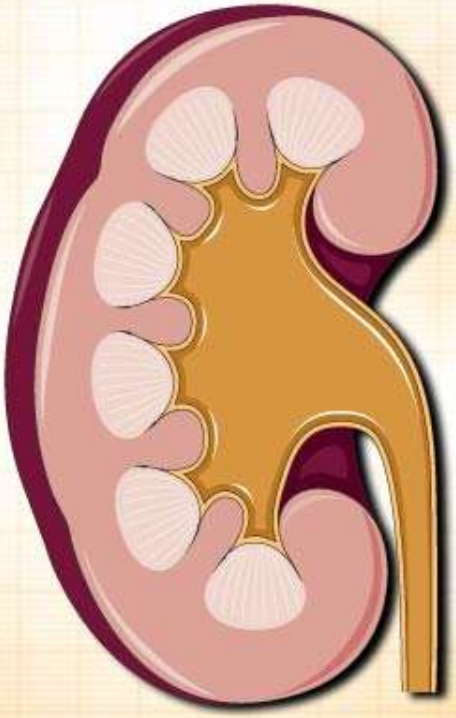
Serum Ca Value or Clinical Symptoms of Hypocalcemia	Recommendations
<8.4 mg/dl (2.1 mmol/L) and >7.5 mg/dl (1.9 mmol/L), or persistent symptoms of hypocalcemia despite attempts to increase serum Ca	Ca-containing P binders, vitamin D sterols, and/or adjustment of dialysis fluid Ca concentrations can be used to raise serum Ca according to clinical judgment
<8.4 mg/dl (2.1 mmol/L) and >7.5 mg/dl (1.9 mmol/L), or in the presence of clinical symptoms of hypocalcemia	Reduce or withhold the dose of cinacalcet
≤7.5 mg/dl (1.9 mmol/L) or persistent symptoms of hypocalcemia and vitamin D cannot be increased	Withhold administration of cinacalcet until serum Ca levels reach 8 mg/dl (2.0 mmol/L) and/or symptoms of hypocalcemia have resolved. Treatment should be reinitiated using the next lowest dose of cinacalcet

Clin J Am Soc Nephrol 11: 161–174, 2016.

Clinical and Practical Use of Calcimimetics in Dialysis Patients With Secondary Hyperparathyroidism

Jordi Bover,† Pablo Ureña,‡§ César Ruiz-García,*† Iara daSilva,*† Patricia Lescano,*† Jacqueline del Carpio,*† José Ballarín,*† and Mario Cozzolino‖*






New!

CALCIMIMETICS.

TYPE I

Mimic the effects of extracellular calcium on CaR

Etelcalcitide

(AMG-416)

TYPE II

Allosteric activators of the CaR, changing its structural conformation and stereoselectively increasing sensitivity to extracellular Ca2+.

Cinacalcet hydrochloride

(AMG-073)

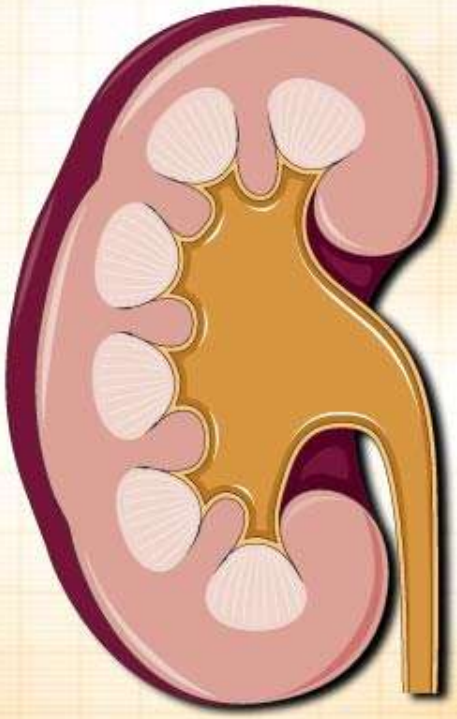
January 26, 2016

Investigational Agent Shows Promise for SHPT in Hemodialysis Patients

AMG416 (etelcalcitide)

Etelcalcitide is a novel peptide agonist of the calcium sensing Receptor; given intravenously thrice weekly starting at 5 mg per session and titrated based on each patient's parathyroid hormone (PTH) and albumin corrected calcium level to target a PTH level of 150–300 pg/mL.

- 37 adult HD Patients had a mean PTH level of 853 pg/mL.
- Patients had a mean 53.6% decrease in PTH level.
- The proportion of patients with a 30% or greater reduction in PTH from baseline was 89%.
- 56% of patients had achieved a PTH level of 300 pg/mL or less.



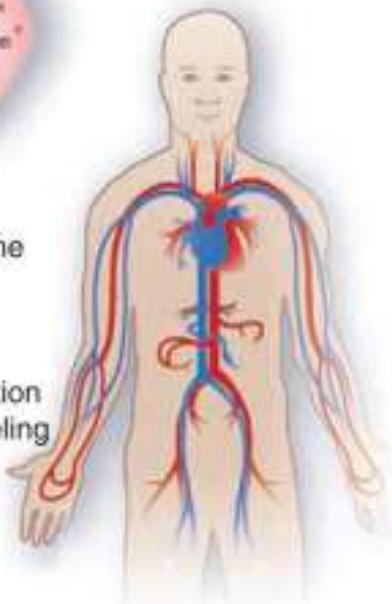
American Journal of Nephrology (2015;42:379388).

Regulates the secretion of PTH and calcitonin

Is involved in a variety of cellular processes:
Gene expression
Proliferation
Dierentiation
Apoptosis
Chemotaxis
Hematopoietic stem cell localization

Promotes divalent ion excretion
Increases free water clearance and polyuria
Possible role in production of calcitriol

Is implicated in the regulation of:
Myogenic tone
Blood pressure
Vascular calcication
Vascular remodeling



Is involved in chondrogenesis and growth plate development

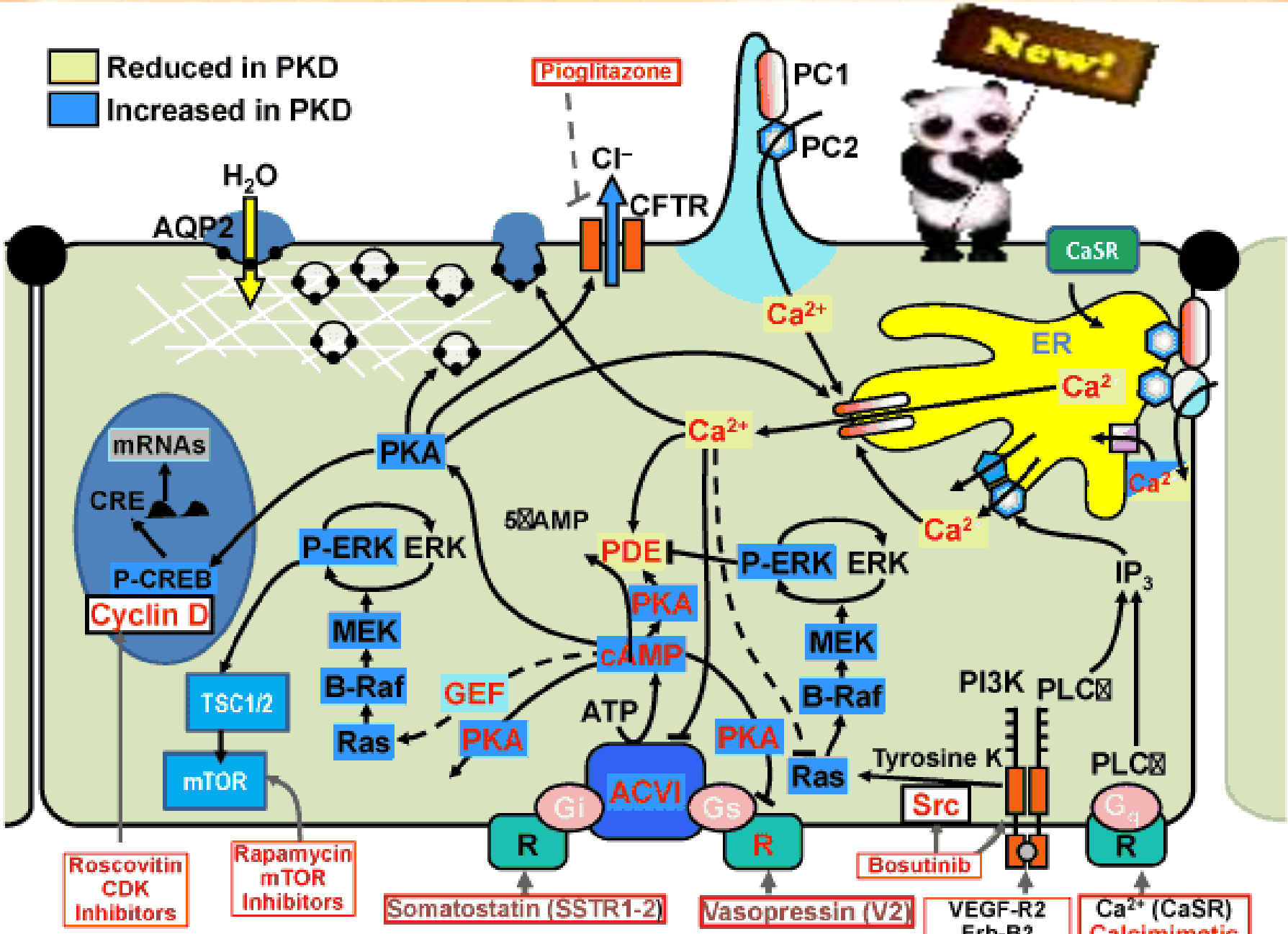
Regulates (possibly initiates) insulin secretion

Controls axon and dendrite outgrowth during development

Functions as an L-amino acid sensor:
Regulates amino acid–dependent gut hormone secretion, epithelial transport, and satiety
Senses the nutritional status of cells

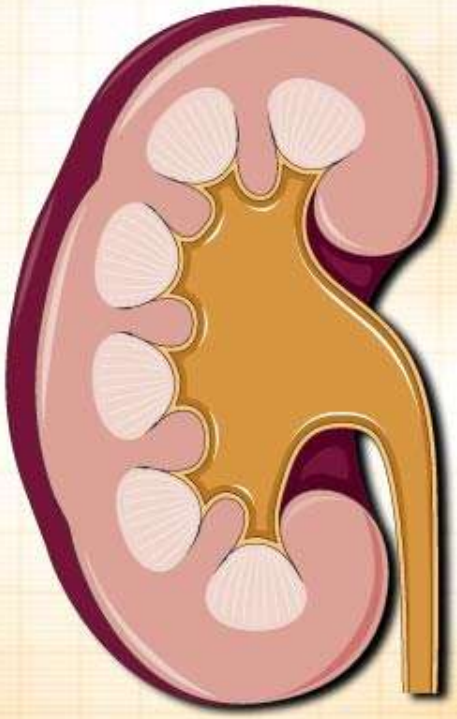
The new role of calcimimetics as vasculotropic agents

Kidney International, Volume 75, Issue 1, 2009, 9–12



Modified from Torres (Adv Chronic Kidney Dis. 2010;17:190-204) **and Gattone et al.,** (Nat Med. 2003;9(10):1323-1326)

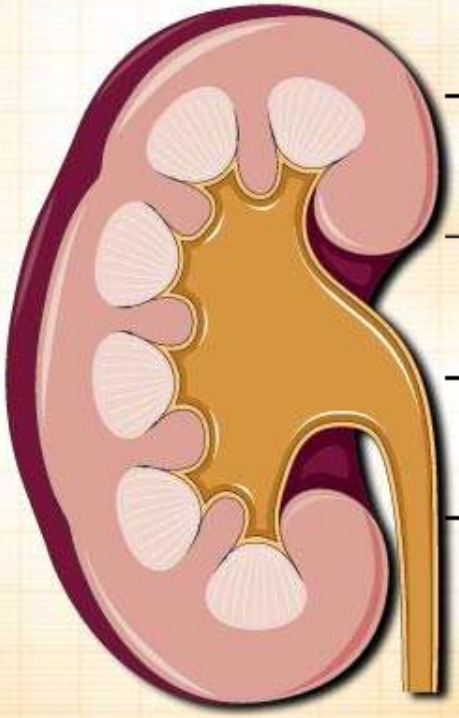
CONCLUSION



Reduction
Slight Reduction
No effect
Increase

Agent	P	Ca	$\frac{Ca}{P}$ ×	iPTH
Vitamin D	↑	↑	↑	↓↓↓
Ca-based PO_4 binders	↓↓	↑↑	↓	↓
Non Ca-based PO_4 binders	↓↓	→	↓	→
Cinacalcet	↓	↓	↓	↓↓↓

- **Calcimimetics are an important option for patients with CKD-MBD and uncontrolled secondary hyperparathyroidism**
  - Help control several biochemical markers, such as serum calcium, phosphate, Ca x P, in addition to iPTH.
  - Recently it has been described that calcimimetics may decrease FGF-23 levels (related with mortality)
  - Allow some patients to decrease the need for high-dose vitamin D derivatives and phosphate binders
  - Provide room for vitamin D derivatives in patients prone to hypercalcaemia or hyperphosphataemia
  - May increase the safe therapeutic window in patients with vascular calcification
  - May be used in patients without severe secondary hyperparathyroidism (specially if they have high serum calcium and phosphorus values)



National Institute for Health and Clinical Excellence. January 2007